

Division of New Drugs
and Labeling
Compliance

Targeted Risk Based
Enforcement

- Internet and Health Fraud Team
- New Drugs and Labeling Team
- Over-the-Counter Drugs Team
- Imports, Exports and PDMA Team
- Compounding Team

Internet and Health
Fraud Team

Risk-Based Assessment and Prioritization

- Prioritize unapproved new drugs identified for regulatory action using risk-based assessment
- Develop compliance strategies to address the most significant legal violations.

“Dietary Supplement” Survey

- Products promoted and sold on websites as "dietary supplements" for treating erectile dysfunction and enhancing sexual performance.
- Undercover buy survey: 17 products sold as “dietary supplements” were purchased and analyzed.
- Six of 17 products contained either sildenafil [approved prescription drug active pharmaceutical ingredient (API)] or an analogue of sildenafil or vardenafil, another API.
- Products: Zimaxx, Libidus, Neophase, Nasutra, Vigor-25, Actra-Rx.

“Dietary Supplement” Survey – Continued

- Significant risk to public health.
- Warning letters were issued to the firms who marketed the products. Libidus and 4EVERON were placed on import alert. A press release was issued.
- Investigations are ongoing.

Hydrogen Peroxide Therapy

- 35% (high-strength) hydrogen peroxide marketed over the internet for oral and IV medicinal uses.
- Claims to treat cancer, emphysema, AIDS, and other serious, life-threatening diseases.
- 35% hydrogen peroxide is not approved by FDA for any purpose.
- Direct health hazard: Reports of serious adverse events, including death.
- Warning letters issued to two firms.
- Press Release



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New Drugs and Labeling Team

Marketed Unapproved Drugs Initiative

- lack rigorous scientific review that demonstrates safety and effectiveness
- labeling may be deficient and not meet contemporary standards
- potentially significant public health issue

Marketed Unapproved Drugs – Compliance Policy Guide

- issued June 2006
- intended to assure that all drugs are safe and effective
- a prioritized, risk-based enforcement approach encouraging companies to independently comply with the approval process
- outlines a risk-based enforcement approach that is flexible, but firm
- prioritization based on potential to harm the public health
- one part of our ongoing drug safety initiative to ensure that patients, consumers, and health-care providers have the most up-to-date drug safety information

Enforcement Priorities

- Drugs with potential safety risks
- Drugs that lack evidence of effectiveness
- Health fraud drugs
- Drugs that present direct challenges to the new drug approval and OTC monograph systems
- Unapproved new drugs that violate the act in other ways (e.g., GMP deficiencies)
- Drugs that are reformulated to evade FDA enforcement action

Initiation Process

- Ongoing assessment of marketed unapproved drugs for risk potential
- Ad hoc assessments
- Action Process
 - Federal Register Notice
 - Administrative Action (Warning Letter)

Enforcement Activity: Examples

Carbinoxamine Action

- DESI reviewed drug, requires approval for marketing
- Two approved carbinoxamine products for various allergic symptoms
- Safety concerns regarding their use in children under 2 years of age.
- Formulated as drops and syrups specifically labeled for use in children as young as one month of age
- Never studied in very young children, and FDA cannot predict how they will respond
- Children under 2 years of age more susceptible to drug-related adverse events, in part due to the immaturity of their systems

The Unapproved Drugs Initiative: Enforcement Activity: Examples

● Drug Manufacturer/Other Violations:

● Syntho/Intermax

- Contract manufacturer
- Inspections detected evidence of multiple cGMP violations and unapproved drugs
- Complaint and Consent Decree signed August 10, 2006
 - Companies and principals agree to cease manufacture and distribution until cGMP compliant, cease marketing unapproved drugs, and recall drugs in distribution pipeline

● Pharmakon Labs

- Inspections revealed cGMP violations and unapproved drugs
- Court-ordered injunction July 25, 2005 barred company from manufacturing until it complies with cGMP standards and obtains approvals

The Unapproved Drugs Initiative: Enforcement Activity: Examples

● **Drug Class: Quinine**

- Drug labeled for malaria; commonly used off-label for leg cramps
 - Serious safety risks, including death, yet unlabeled versions omitted clinically essential safety warnings regarding adverse events, contraindications, and drug interactions
 - Narrow therapeutic margin, yet dosing for unapproved versions not reviewed by FDA
- One approved NDA – Mutual Pharmaceutical Co., Inc., approved 8/12/2005
- Federal Register notice December 15, 2006: firms must cease manufacturing unapproved quinine by February 13, 2007, shipment in interstate commerce must cease by June 13, 2007

The Unapproved Drugs Initiative: Enforcement Activity: Examples

- **Warning Letters:** Many issued – see the unapproved drugs web page for list, http://www.fda.gov/cder/drug/unapproved_drugs
- **Ergotamine-Containing Products** Warning Letters, March 2007
 - vascular headaches
 - Box Warning: Approved products have a boxed warning against use of ergotamine with certain antibiotics & other drug products

Over-the-Counter Drugs Team

OTC Enforcement Priorities

- Products that present a health hazard
- Products that violate the integrity of the OTC monograph process or the NDA process

Selected OTC Priorities

- Nail Fungus Products
- Topical Hormone Products
- Cough/Cold Combination Products
- Barrier Cream Products

Recent Enforcement Action

- Triaminic Vapor Patch (cough/cold relief)
To be used on children 2 yrs. to 12 yrs. of age
- Ingredients met the final monograph,
but patch dosage form did not
- Child could remove patch and ingest drug
ingredients
- Class I health hazard – product was recalled

Import-Export Team

Import-Export Team

- Agency focal point for all compliance issues that involve the import and export of drug products in the U.S.
- Enforces the laws and regulations under the Prescription Drug Marketing Act (PDMA) and implementing related regulatory policies.

Import- Export Team

Team Priority: Secure Supply Chain (SSC)

- To facilitate entry review of compliant products under a secure supply chain program.
- Pilot program will be used to evaluate feasibility and benefits of the program.
- Requires manufacturers to provide certain product information from the foreign manufacturing sites to the U.S. distribution centers.

Import- Export Team

SSC

This information includes:

- API source, intermediate manufacturing steps, storage, packaging and labeling processes, methods of transportation from the foreign manufacturing site to the foreign port of loading and into the U.S. port of entry; and methods of transportation from the port of entry to the U.S. consignee.

Import-Export Team

Advantages of a secure supply chain:

- Protects against terrorism, counterfeiting, and diversion activities in imported products.
- FDA can verify and/or audit all data.
- Agency can focus its resources on the review of non-complaint products that can pose a risk to U.S. consumers.

The Compounding Team (TCT)

The Compounding Team Priorities

- Compounding vs Manufacturing
- Copying commercially available drugs
- Risks to public health
- False and misleading internet claims

The Compounding Team Priorities

- Compounding vs Manufacturing
- Copying commercially available drugs
 - e.g. Inhalation drugs
 - CMS reimbursement
 - Sterility requirement, inappropriate compounding
 - Recent Warning Letters

The Compounding Team Priorities

- Risks to public health
 - e.g. Local Anesthetics
- High percentage
- Combinations
- Lack of instructions
- Recent Warning letters

The Compounding Team Priorities

- False and misleading internet claims
 - Clinical Superiority
 - Cure for life threatening diseases